# U.S. Preventive Services Task Force

## Screening for Thyroid Dysfunction: Recommendation Statement

As published by the U.S. Preventive Services Task Force.

This summary is one in a series excerpted from the Recommendation Statements released by the USPSTF. These statements address preventive health services for use in primary care clinical settings, including screening tests, counseling, and preventive medications.

The complete version of this statement, including supporting scientific evidence, evidence tables, grading system, members of the USPSTF at the time this recommendation was finalized, and references, is available on the USPSTF website at http://www.uspreventiveservicestaskforce.org/.

This series is coordinated by Sumi Sexton, MD, Associate Medical Editor.

A collection of USPSTF recommendation statements published in *AFP* is available at http://www.aafp.org/afp/uspstf.

### Summary of Recommendation and Evidence

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults *(Table 1)*. **I statement.**

See the Clinical Considerations section for suggestions for practice regarding the I statement.

### Rationale

#### IMPORTANCE

Thyroid gland disorders are among the most common endocrine conditions evaluated and treated by clinicians. Thyroid dysfunction represents a continuum from asymptomatic biochemical changes to clinically symptomatic disease. In rare cases, it can produce life-threatening complications, such as myxedema coma or thyroid storm.[1,2]

*Subclinical hypothyroidism* is defined as an asymptomatic condition in which a patient has a serum thyroid-stimulating hormone (TSH) level exceeding the upper threshold of a specified laboratory reference interval (commonly but arbitrarily defined as 4.5 mIU/L) but a normal thyroxine (T4) level.[3] Patients with subclinical hypothyroidism are often further classified as having TSH levels between 4.5 and 10.0 mIU/L or greater than 10.0 mIU/L.

Despite its name, "*overt*" *hypothyroidism* does not require the presence of symptoms and has been defined biochemically by an elevated TSH level and a low T4 level. As such, it encompasses a range of low T4 levels that may (or may not) be associated with a set of relatively subtle and nonspecific clinical symptoms, such as fatigue, feeling cold, weight gain, hair loss, and constipation.

*Subclinical hyperthyroidism* is defined as an asymptomatic condition in which a patient has a serum TSH level below the lower threshold of a specified laboratory reference interval (usually 0.4 mIU/L) but normal T4 and triiodothyronine (T3) levels. Patients with subclinical hyperthyroidism are further classified as having "low but detectable" (about 0.1 to 0.4 mIU/L) or "clearly low" or "undetectable" (< 0.1 mIU/L) TSH levels.[3]

Despite its name, "*overt*" *hyperthyroidism* does not require the presence of symptoms and has been defined biochemically by a low or undetectable TSH level and an elevated T4 or T3 level. When present, symptoms are often relatively nonspecific (for example, weight loss, heart palpitations, heat intolerance, and hyperactivity).

For the purposes of this recommendation, *thyroid dysfunction* is defined as a spectrum of disorders related to the thyroid gland. The spectrum begins with asymptomatic subclinical hypothyroidism and hyperthyroidism. In the middle of the spectrum are asymptomatic "overt" hypothyroidism and hyperthyroidism, defined biochemically by changes in serum TSH and T4 levels. At the end of the spectrum is thyroid disease, which is reserved for symptomatic "overt" hypothyroidism and hyperthyroidism (that is, persistently abnormal serum TSH and T4 levels and clearly associated clinical signs and symptoms that cannot be better explained by another condition).

In making its recommendations about clinical preventive services, the USPSTF focuses on asymptomatic populations that do not have known signs or symptoms of disease.

#### DETECTION

Early detection and treatment of asymptomatic persons with abnormal serum TSH levels with or without abnormal T4 levels

**Table 1. Screening for Thyroid Dysfunction: Clinical Summary of the USPSTF Recommendation**

| | |
|---|---|
| Population | Nonpregnant, asymptomatic adults |
| Recommendation | No recommendation<br>Grade: I statement (insufficient evidence) |
| Risk assessment | Risk factors for an elevated thyroid-stimulating hormone (TSH) level include female sex, advancing age, white race, type 1 diabetes, Down syndrome, family history of thyroid disease, goiter, previous hyperthyroidism, and external-beam radiation in the head and neck area. Risk factors for a low TSH level include female sex; advancing age; black race; low iodine intake; personal or family history of thyroid disease; and ingestion of iodine-containing drugs, such as amiodarone. |
| Screening tests | The primary screening test for thyroid dysfunction is serum TSH testing. Multiple tests over 3 to 6 mo should be performed to confirm or rule out abnormal findings. Follow-up testing of serum thyroxine (T4) levels in persons with persistently abnormal TSH levels can differentiate between subclinical (normal T4) and "overt" (abnormal T4) thyroid dysfunction. |
| Treatment and interventions | Hypothyroidism is treated with oral T4 monotherapy (levothyroxine sodium). Consensus is lacking on the appropriate point for clinical intervention, especially for TSH levels < 10.0 mIU/L. Hyperthyroidism is treated with antithyroid medications (e.g., methimazole) or nonreversible thyroid ablation therapy (e.g., radioactive iodine or surgery). Treatment is generally recommended for patients with a TSH level that is undetectable or < 0.1 mIU/L, particularly those with overt Graves disease or nodular thyroid disease. |
| Balance of benefits and harms | The current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant asymptomatic adults. |

NOTE: *For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, go to http://www.uspreventiveservicestaskforce.org/.*

*USPSTF = U.S. Preventive Services Task Force.*

may be beneficial because it may prevent longer-term morbidity and mortality from fractures, cancer, or cardiovascular disease. However, widespread screening and treatment of subclinical thyroid dysfunction can also result in harms due to labeling, false-positive results, and overdiagnosis and overtreatment.

The USPSTF found adequate evidence that screening can detect "abnormal" serum TSH levels in asymptomatic persons. However, what constitutes an abnormal TSH level is uncertain. Laboratory reference intervals are based on the statistical distribution of TSH levels across the general population (for example, using the 97.5th percentile as an upper boundary for normal) rather than according to the association of a TSH level with symptoms, adverse outcomes, or particular risk factors for disease.[3] There is professional disagreement about the appropriate cut points for the lower and upper boundaries of normal TSH levels in the general population and in subgroups, such as older adults, where values differ from the overall population distribution (for example, shifting to a higher range of normal).[4-7]

Accurate interpretation of serum TSH levels is further complicated by measurement variability and the sensitivity of TSH secretion to conditions other than thyroid dysfunction. These issues have led many professional groups to recommend repeating thyroid function tests if the results fall above or below a specified reference interval for confirmation of persistent dysfunction (for example, over 3- to 6-month intervals) in asymptomatic persons before making a diagnosis or considering any treatment strategies, unless the serum TSH level is greater than 10.0 or less than 0.1 mIU/L.[3,8,9]

### BENEFITS OF EARLY DETECTION AND TREATMENT

The USPSTF found inadequate evidence that screening for thyroid dysfunction in nonpregnant, asymptomatic adults leads to

clinically important benefits. In particular, the USPSTF found inadequate evidence to determine whether screening for thyroid dysfunction reduces cardiovascular disease or related morbidity and mortality.

The USPSTF found adequate evidence that screening for and treatment of thyroid dysfunction in nonpregnant, asymptomatic adults does not improve quality of life or provide clinically meaningful improvements in blood pressure, body mass index (BMI), bone mineral density, or lipid levels. It also does not improve cognitive function, at least through the duration of available trials (≥ 1 to 2 years).[1,2]

#### HARMS OF EARLY DETECTION AND TREATMENT

The USPSTF found inadequate evidence on the harms of screening for and treatment of thyroid dysfunction. Indirect evidence points to the likelihood of important and frequent harms associated with screening in asymptomatic persons. Foremost among these are frequent false-positive results; the psychological effects of labeling; and a large degree of overdiagnosis and overtreatment of biochemically defined abnormal TSH levels (with or without abnormal serum T4 levels) that may revert to normal, not progress, or never result in health problems even if they do progress, particularly in persons with TSH levels less than 10 mIU/L.

#### USPSTF ASSESSMENT

The USPSTF concludes that the evidence is insufficient and that the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults cannot be determined.

If clinicians offer screening for thyroid dysfunction to asymptomatic persons, they should first ensure that patients clearly understand the uncertainties surrounding any potential clinical benefit of screening as well as the possibility of harm this choice may engender.

## Clinical Considerations

#### PATIENT POPULATION UNDER CONSIDERATION

This recommendation applies to nonpregnant, asymptomatic adults.

#### SUGGESTIONS FOR PRACTICE REGARDING THE I STATEMENT

*Potential Preventable Burden*. About 5% of women and 3% of men in the United States have subclinical hypothyroidism.[4] Of note, several studies have shown that about 37% of persons with subclinical hypothyroidism spontaneously revert to a euthyroid state without intervention after several years.[10,11] About 2% to 5% of persons with subclinical hypothyroidism develop "overt" thyroid dysfunction.[12]

One retrospective cohort study found that levothyroxine use in persons with subclinical hypothyroidism was associated with lower risk for ischemic heart disease events and overall mortality[13]; however, the USPSTF did not identify any clinical trials that evaluated the causal relationship between treatment and subsequent cardiac events. The USPSTF did not identify any trials or observational studies that evaluated the effects of treatment of "overt" hypothyroidism (with or without symptoms) versus no treatment.

Subclinical hyperthyroidism is present in about 0.7% of the U.S. population and is more common in women than men.[4] One-quarter of persons with subclinical hyperthyroidism revert to a euthyroid state without medical intervention over time.[10,14] An estimated 1% to 2% of persons with TSH levels less than 0.1 mIU/L develop "overt" hyperthyroidism (with or without symptoms). Persons with TSH levels between 0.1 and 0.45 mIU/L are unlikely to progress to "overt" hyperthyroidism.[8]

The USPSTF did not identify any studies that evaluated the benefits of treatment of subclinical hyperthyroidism on final health outcomes, such as fractures, cancer, or cardiovascular morbidity or mortality. Except for 1 small ($n$ = 67) nonrandomized study that examined bone mineral density, no evidence was found on the effects of treatment of "overt" hyperthyroidism (with or without symptoms).[1,2]

*Potential Harms*. The harms of treatment of thyroid dysfunction have not been well studied. The most important potential harms are false-positive results, labeling, and overdiagnosis and overtreatment.

False-positive results occur because TSH secretion is highly variable and sensitive to

several common factors, such as acute illness or certain medications. Ascertainment of true- versus false-positive results is further complicated by a lack of consensus on what constitutes a normal reference interval.

Consensus is also lacking on the appropriate point for clinical intervention, particularly for hypothyroidism. No clinical trial data support a treatment threshold to improve clinical outcomes. On the basis of expert opinion, a TSH level greater than 10.0 mIU/L is generally considered the threshold for initiation of treatment (in part because of the higher likelihood of progression to "overt"—even if still asymptomatic—thyroid dysfunction). The decision of whether and when to begin therapy in patients with TSH levels between 4.5 and 10.0 mIU/L is more controversial.[3,15] A large magnitude of overdiagnosis and overtreatment is a likely consequence of screening for thyroid dysfunction, particularly because the disorder is defined by silent biochemical parameters rather than a set of reliable and consistent clinical symptoms. The high variability of TSH secretion levels and the frequency of reversion to normal thyroid function without treatment underscore the importance of not relying on a single abnormal laboratory value as a basis for diagnosis or the decision to start therapy.

Currently, it is not possible to differentiate persons who will have advancing thyroid dysfunction of clinical importance from those whose TSH levels will remain biochemically stable or even normalize. Treating the latter group (at a minimum) will not lead to benefit, and these persons may experience harms associated with antithyroid medications, ablation therapy, and long-term thyroid hormone therapy.

*Current Practice.* Although exact estimates are not available for the United States, screening for thyroid dysfunction by primary care providers seems to be a common practice.[16] In the United Kingdom, an estimated 18% to 25% of the adult population receives thyroid function testing each year.[17]

The annual number of dispensed prescriptions of levothyroxine sodium in the United States increased by 42% over a 5-year period, from 50 million in 2006 to 71 million in 2010.[18] In 2013, there were more than 23 million new prescriptions and refills for a single name brand of thyroid hormone in the United States, making it the most commonly prescribed drug in the country.[19]

In 1996, a cross-sectional study of a U.S. population found that 39% of participants with TSH levels between 5.1 and 10.0 mIU/L received treatment.[20] More recent evidence suggests that the median TSH level at initiation of thyroid hormone therapy has decreased over time; a retrospective cohort study in the United Kingdom found that the median TSH level at the time of first levothyroxine prescription decreased from 8.7 to 7.9 mIU/L between 2001 and 2009.[17]

Initiation and use of thyroid hormone therapy seem to be particularly common in older adults. Data from the CHS (Cardiovascular Health Study), a U.S. cohort of nearly 6,000 community-dwelling adults aged 65 years or older, showed a steady increase in the overall percentage of older adults receiving thyroid hormone therapy (from 9% in 1989 to 20% in 2006) and a nonlinear probability of initiating levothyroxine therapy based on age; persons aged 85 years or older were more than twice as likely as those aged 65 to 69 years to begin thyroid hormone therapy (hazard ratio [HR], 2.34 [95% CI, 1.43 to 3.85]), independent of race or sex.[21]

Data on the proportion of asymptomatic persons with thyroid dysfunction who receive thyroid hormone therapy are lacking. However, given the high number of prescriptions for levothyroxine dispensed in the United States and the low prevalence of "overt" hypothyroidism and hyperthyroidism among persons in the general population (0.3% and 0.5%, respectively,[4] only a small fraction of whom are symptomatic), it is reasonable to conclude that many asymptomatic persons receive treatment. Clinicians seem to be treating more persons with thyroid dysfunction, at earlier times after initial diagnosis, and at TSH levels closer to normal.

### ASSESSMENT OF RISK

The most common cause of hypothyroidism in the United States is chronic autoimmune (Hashimoto) thyroiditis. Risk factors for an elevated TSH level include female sex, advancing age, white race, type 1 diabetes, Down syndrome, family history of thyroid disease, goiter, previous hyperthyroidism (possibly

due in part to ablation therapy leading to iatrogenic thyroid dysfunction), and external-beam radiation in the head and neck area.[1,2]

Common causes of hyperthyroidism include Graves disease, Hashimoto thyroiditis, and functional thyroid nodules. Risk factors for a low TSH level include female sex; advancing age; black race; low iodine intake; personal or family history of thyroid disease; and ingestion of iodine-containing drugs, such as amiodarone.[1,2]

The USPSTF found no direct evidence that treatment of thyroid dysfunction based on risk level alters final health outcomes.

### SCREENING TESTS

The serum TSH test is the primary screening test for thyroid dysfunction. Multiple tests should be done over a 3- to 6-month interval to confirm or rule out abnormal findings. Follow-up testing of serum T4 levels in persons with persistently abnormal TSH levels can differentiate between subclinical (normal T4 levels) and "overt" (abnormal T4 levels) thyroid dysfunction.

### SCREENING INTERVAL

The optimal screening interval for thyroid dysfunction (if one exists) is unknown.

### INTERVENTIONS

The principal treatment for hypothyroidism is oral T4 monotherapy (levothyroxine sodium).

Hyperthyroidism is treated with antithyroid medications (such as methimazole) or nonreversible thyroid ablation therapy (for example, radioactive iodine or surgery). Although definitive data are lacking, treatment is generally recommended for patients with a TSH level that is undetectable or less than 0.1 mIU/L, particularly those with overt Graves disease or nodular thyroid disease. Treatment is typically not recommended for patients with TSH levels between 0.1 and 0.45 mIU/L or when thyroiditis is the cause.[1,2]

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The "Other Considerations," "Discussion," "Update of Previous USPSTF Recommendation," and "Recommendations of Others" sections of this recommendation statement are available at http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/thyroid-dysfunction-screening.



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